AD-A167 738 ALTITUDE ACCLIMATIZATION (VENTILATION AND CHEMORESPONSIVENESS) DURING WAK.. (U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA D P WHITE ET AL. 1/1

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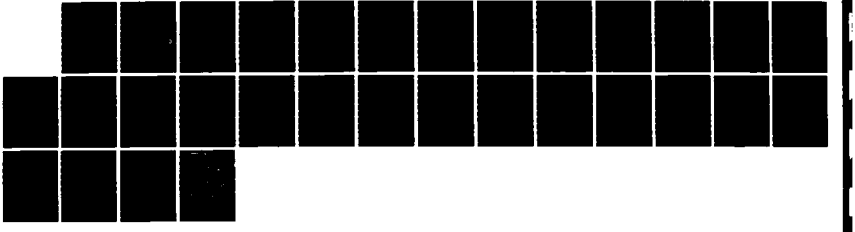

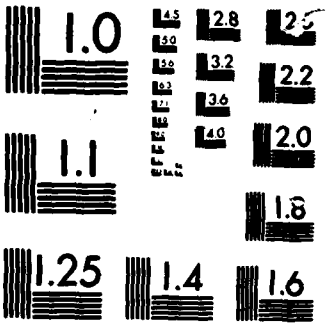

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Although the influence of altitude acclimatization on respiration has been carefully studied, the associated changes in hypoxic and hypercapnic ventilatory responses are the subject of controversy and neither response has been carefully evaluated during sleep at altitude. To answer these questions, six healthy males were studied at sea level and on nights 1, 4, and 7 following arrival at altitude (14,110 ft). During wakefulness ventilation and the ventilatory responses to hypoxia and hypercapnia were determined on each occasion. During both NREM and REM sleep at sea level and on all three nights at altitude,

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ventilation and the hypercapnic ventilatory response were measured. With acclimatization to high altitude ventilation increased during both wakefulness and sleep which reflected primarily increasing respiratory frequency. The hypoxic response, although not significantly increased on day 1 at altitude, rose steadily over subsequent days on the mountain (P less than 0.01). The slope of the hypercapnic response, although initially increased at altitude (day 1), did not rise further with acclimatization although the position of this response shifted significantly to the left during wakefulness and sleep. Finally, sleep induced similar decrements in both ventilation and hypercapnic responsiveness at altitude to those seen at sea level. These observations suggest that: (1) hypoxic sensitivity increases with time at altitude and could be an important contributor to ventilatory acclimatization, (2) that the hypercapnic response, although shifted to the left, does not increase in slope with prolonged exposure to hypoxia and (3) that acclimatization produces similar effects on ventilation and hypercapnic responsiveness during sleep to those observed during wakefulness.

Key words: Rapid Eye Movement Sleep

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TITLE: ALTITUDE ACCLIMATIZATION (VENTILATION AND CHEMORESPONSIVENESS) DURING WAKEFULNESS AND SLEEP

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ABBREVIATED TITLE: Altitude Acclimatization

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ABSTRACT

Although the influence of altitude acclimatization on respiration has been carefully studied, the associated changes in hypoxic and hypercapnic ventilatory responses are the subject of controversy and neither response has been carefully evaluated during sleep at altitude. To answer these questions, six healthy males were studied at sea level and on nights 1,4, and 7 following arrival at altitude (14,110 ft). During wakefulness ventilation and the ventilatory responses to hypoxia and hypercapnia were determined on each occasion. During both NREM and REM sleep at sea level and on all three nights at altitude, ventilation and the hypercapnic ventilatory response were measured. With acclimatization to high altitude ventilation increased during both wakefulness and sleep which reflected primarily increasing respiratory frequency. The hypoxic response, although not significantly increased on day 1 at altitude, rose steadily over subsequent days on the mountain ($P<0.01$). The slope of the hypercapnic response, although initially increased at altitude (day 1), did not rise further with acclimatization although the position of this response shifted significantly to the left during wakefulness and sleep. Finally, sleep induced similar decrements in both ventilation and hypercapnic responsiveness at altitude to those seen at sea level. These observations suggest that: (1) hypoxic sensitivity increases with time at altitude and could be an important contributor to ventilatory acclimatization, (2) that the

hypercapnic response, although shifted to the left, does not increase in slope with prolonged exposure to hypoxia and (3) that acclimatization produces similar effects on ventilation and hypercapnic responsiveness during sleep to those observed during wakefulness.

Index Terms: Acclimatization, Hypoxic and Hypercapnic Ventilatory Responses, Non-REM and REM Sleep, Altitude.

INTRODUCTION

Although the influence of altitude acclimatization on the ventilatory responses to chemical stimuli has been the focus of considerable investigation over many years (5,10,13,17,18,20, 21), there remain a number of unresolved questions regarding chemoresponsiveness. First, the affect of acclimatization on the hypoxic ventilatory response has been minimally studied with no clear indication how this response is influenced by sustained hypoxia (5,13,17). This seems an important question as augmented hypoxic sensitivity could, in part, explain the well described increase in ventilation that occurs with time at altitude despite decreasing P_{CO_2} and increasing arterial oxygen saturation.

The influence of altitude acclimatization on hypercapnic responsiveness is also somewhat in question. It seems clear that the position of this response shifts to the left (lower P_{CO_2} level) with acute hypoxia and continues to shift with time at altitude (10,13,17,20,21). However, the effect of acclimatization on the slope of this response is less clear. Acute hypoxia increases the slope of the hypercapnic response as the combination of hypoxia and hypercapnia is a more powerful stimulus to ventilation than either chemical drive alone (14). However, whether the slope increases further over time in an hypoxic environment remains unresolved (5,10,13,17,20,21). In addition, the effect of sleep on the hypercapnic ventilatory response both in acute hypoxia and with progressive acclimatization has not been investigated.

In order to answer the above questions regarding the influence of altitude acclimatization on chemoresponsiveness and in so doing to obtain further information on ventilatory acclimatization both awake and asleep, the following studies were undertaken.

METHODS

The description of subject characteristics, equipment, and techniques for the measurement of ventilatory responses to hypoxia (HVR) and hypercapnia (HCVR) under all desired conditions are described in the companion article (24). To summarize, six healthy males were studied both at sea level and altitude. At sea level, during wakefulness and NREM sleep, measurement of the hypoxic and hypercapnic ventilatory responses was completed. During REM sleep only the hypercapnic response was measured. The subjects were then transported to Pikes Peak (altitude 14,110 ft, barometric pressure, 460 mmHg) and studied on nights 1,4, and 7 after arrival. During wakefulness, prior to sleep on each occasion, hypoxic and hypercapnic ventilatory responses were completed. During NREM and REM sleep on each night only the HCVR was measured. The mean number of hypercapnic response determinations completed awake and asleep, at sea level and on each night at altituide are given in Table 1. In addition to the above studies, a final awake hypoxic ventilatory response was conducted on day 19 at altitude. All other studies ended after night 7. Finally, an additional subject, subject 7 who did not participate in the above sleep studies, did have awake HVR measurements made on all occasions described above. As a result,

data concerning the influence of altitude acclimatization on hypoxic sensitivity will include this additional subject.

The hypoxic ventilatory response will be described as the slope of increasing ventilation versus decreasing arterial oxygen saturation. These hypoxic responses were measured isocapnically at the P_{CO_2} level present when the subject had an arterial oxygen saturation of 99-100%. In describing the hypercapnic ventilatory response two values are generally reported; the slope of the response (S) and the intercept of this line on the P_{CO_2} axis (B). This B is generally used to describe the position of the response but is dependent on both the position and slope of this curve. For this reason we will report the position of the HCVR as the P_{CO_2} level at which ventilation is initially stimulated by increasing P_{CO_2} (Figure 1, the P_{CO_2} stimulation point). This point was determined by extrapolating the steep portion of the hypercapnic response to the "resting ventilation line" where ventilation is not stimulated by increasing P_{CO_2} (Figure 1). Using this method, the influence of slope on curve position is minimized.

Resting Ventilation:

In conjunction with the above studies, the following determinations of resting ventilation were completed. During unstimulated breathing, awake and asleep, at sea level and altitude, ventilation and its components were measured. These consisted of $\dot{V}_E$ (expired ventilation), V_T (tidal volume), f (frequency), $P_{ET}CO_2$, and SaO_2 (arterial oxygen saturation).

Generally, three breath averages of all variables were determined on a Data General Nova 4 computer (Data General, Westboro, MA.) in real time. During periodic breathing at altitude, however, end-tidal P_{CO_2} was determined for each breath.

At sea level awake ventilation was measured for 5 minutes prior to sleep onset and for an additional 5 minutes after final awakening. During sleep (sea level) unstimulated ventilation was recorded repetitively in 3 to 15 minute time blocks in isolated sleep stages (NREM and REM). At altitude, on nights one, four, and seven after arrival, unstimulated ventilation was again monitored for 5 minutes prior to sleep onset during documented wakefulness and repeated in 3 to 15 minute time periods during both NREM and REM sleep. We were able to obtain (in each subject, on each night) 5 minutes of unstimulated ventilation in the waking state, a mean of 26.2±2.2 minutes during NREM sleep and 9.7±1.0 minutes during REM sleep. Again, the equipment and methods employed to determine sleep stages and ventilation are described in the companion article (24).

Data Analysis:

The effect of acclimatization on ventilation and the hypercapnic ventilatory response were analyzed with a two-way analysis of variance (22). This analysis was also employed in evaluating the influence of the various sleep stages on these ventilatory variables. To determine the effect of altitude acclimatization on the hypoxic ventilatory response, a nonparametric Spearman Rank Correlation for monotonic trend (not necessarily linear) between HVR and time at altitude was

used. The statistical confidence interval selected for all analyses was $P < 0.05$.

RESULTS

Ventilation

Ventilation, P_{CO_2}, and arterial oxygen saturation during wakefulness and sleep (NREM and REM) at sea level and altitude (nights 1,4, and 7) are shown in Figure 2. As described previously in sea level studies, ventilation fell from wakefulness to NREM and REM sleep with increasing P_{CO_2} and decreasing $Sa0_2$. This also occurred at altitude and was observed clearly on nights 4 and 7. This decrement in ventilation that occurred from wakefulness to sleep tended to be a result of falling tidal volume (Fig 3). This was consistant at sea level and tended to be true at altitude also, although breathing pattern varied considerably between subjects in relation to the quantity of periodic breathing. However, the increase in ventilation that occurred from sea level to altitude and progressed with time at altitude resulted largely from increasing frequency with little change in tidal volume (Fig 3). There was no difference observed between NREM and REM sleep for any of these ventilatory variables.

On night 1 at altitude, a trend towards increasing ventilation and decreasing $P_{ET}CO_2$ was observed over the course of the night such that the effects of sleep were obscurred and no significant difference in any of these variables ($\dot{V}_E$, $P_{ET}CO_2$, $Sa0_2$) could be detected. This indicates that acclimatization was likely occurring during sleep on this first night at altitude.

This effect was clear in four subjects who demonstrated decreasing $P_{ET}CO_2$ over the course of the study as shown in Figure 4. This event is shown in detail for both ventilation and $P_{ET}CO_2$ in subject 6 (Fig 4). In two subjects no such effect was noted.

The effects of acclimatization on ventilation were clear both awake and asleep. During wakefulness, ventilation steadily increased over 7 days at altitude with falling P_{CO_2} and increasing SaO_2 (Fig 2). During both NREM and REM sleep a similar trend occurred with significantly decreasing $P_{ET}CO_2$ and increasing SaO_2 during both sleep stages over the seven days (Fig 2). However, we were unable to demonstrate a significant increase in ventilation from night 1 to night 4 or 7.

Ventilatory Responses to Chemical Stimuli

Hypercapnia:

NREM and REM sleep reduced the hypercapnic ventilatory response and this effect was consistant at sea level and on all three nights at altitude (Table 1, Fig 5). The NREM hypercapnic response was reduced to approximately 50% ($P<0.05$) of the awake value with the REM response being only about 20% ($P<0.05$) of the awake value. Although this response tended to be lower during REM than the NREM sleep, this did not reach statistical significance.

The effect of altitude on the hypercapnic ventilatory response is also shown in Table 1 and Figure 5. The slope of the hypercapnic response increased significantly when the subjects were initally exposed to altitude (Table 1). However, this increase was observed only during wakefulness and NREM sleep.

During REM sleep the HCVR did not increase over the sea level value (Table 1). With acclimatization the slope of the CO_2 response did not increase further. However, as is shown in Figure 5 and Table 2, there was a progressive leftward shift in the position of the hypercapnic response from sea level to day 1 at altitude and from day 1 to day 4 with no further position change for this response noted after day 4 at altitude (Table 2). This was true during wakefulness and NREM and REM sleep (Table 2).

Hypoxia:

The influence of altitude and acclimatization to altitude on the isocapnic hypoxic ventilatory response are shown on Table 3 and Figures 6 and 7. Although acute exposure to altitude (night 1 studies) did not produce a significant increase in hypoxic sensitivity over that observed at sea level, the slope of the hypoxic response increased steadily and significantly with time at altitude ($P<.001$, Spearman Rank Correlation). This increase in the slope of the hypoxic ventilatory response occurred despite the studies being conducted at progressively lower P_{CO_2} levels.

DISCUSSION

Acclimatization is clearly associated with changes in the hypoxic and hypercapnic ventilatory responses. The hypercapnic response was increased on day 1 at altitude compared to sea level but did not increase further with time. However, the position of this response shifted significantly to the left with acclimatization both awake and asleep (Fig 5 and Table 2). The hypoxic ventilatory response, although not significantly higher on day 1 at altitude than at sea level, increased steadily

with acclimatization (Table 3, Figures 6 and 7). In addition, the sleep induced changes in both resting ventilation and the hypercapnic ventilatory responsive at altitude are similar to those seen at sea level (9). Ventilation falls during both NREM and REM sleep as a result of decreasing tidal volume (Fig 2) while the HCVR is reduced about 50% during NREM sleep and 80% during REM sleep at altitude as we and others observed at sea level (8).

The influence of altitude acclimatization on ventilatory chemical responsiveness has been a topic of interest for years. Our observations regarding the effect of acclimatization on hypoxic sensitivity agree with finding of a number of previous investigators (5,13). Forster et at (13) observed an increase in the HVR at altitude, but this response in their subjects remained elevated 45 days after returning to sea level making the actual baseline hypoxic sensitivity somewhat questionable. Cruz et al (5) also noted an increase in the hypoxic response in 4 subjects over 75 hours at altitude. However, this response was only significantly increased at 75 hours and these subjects were not observed to hyperventilate or decrease their P_{CO_2} over the first 3 hours of hypoxia. These data are therefore, difficult to interpret. Our observations suggests that the HVR increases progressively at altitude even to the 19th day.

This steady increase in hypoxic responsiveness may be an important contributor to the gradual increase in ventilation at high altitude which occurs despite a lower P_{CO_2} and higher arterial oxygen saturation. The recent study of Busch et al. (4)

demonstrated acute (6-8 hours) ventilatory acclimatization in goats when only the isolated carotid body was made hypoxic. This suggests an important role for the carotid body in this process. In addition, other investigators have demonstrated that ventilatory acclimatization is diminished or absent in carotid denervated animals (11,12,18) although this is somewhat controversial (23). Therefore, increasing gain of this chemoreceptor may be a pivotal mechanism in altitude acclimatization.

We could be faulted for determining these hypoxic responses at the P_{CO_2} level measured during a hyperoxic baseline (our studies being conducted at the P_{CO_2} level encountered when the subject had an $Sa0_2$ of 99 to 100%). This seemed, however, the most reasonable approach. To have completed the studies at the eupnic P_{CO_2} level would have meant doing half the study poikiolocapnically (to the eupnic $Sa0_2$ level) and the remaining half with CO_2 addition. This is likely to have produced a biphasic response that would be difficult to interpret. To have conducted the entire study poikilocapnically (no CO_2 addition) would likely have produced a sufficiently blunted response that comparisons would have been difficult. We therefore chose the method described and believe it to be the best of the available options.

Our observed increase in the hypercapnic ventilatory response on arrival at altitude probably reflects the well described potentiating effects of hypoxia on the hypercapnic response (14). With acclimatization we found no further increase

in HCVR but a shift in the response to the left did occur (Fig 5 and Table 2). This left shift is similar to that found in most previous reports (10,13,17,20,21), however, the effect of altitude acclimatization on the slope of this response is contraversial. Most previous studies of HCVR in humans suggest an increase in the slope of this response over time at altitude (10,13,20). Other studies, one in goats (21) and another in humans (5), found no change in this slope. In reviewing these studies it is frequently difficult to differentiate the effects of acute hypoxia from those of acclimatization on the HCVR. Forester et al (13) found a progressive increase in the slope of the hypercapnic response (measured at high P_{O_2}) following 4 and 45 days of altitude exposure. Other investigators (10,17,20) found that acute hypoxia clearly increases the ventilatory resonse to hypercapnia, but the evidence for further augmentation of this response with continued hypoxic exposure is less clear.

No previous investigator, to our knowledge, has measured this response as we did with a constant arterial oxygen saturation maintained at the eupnic level. This method was chosen such that comparisons between awake and sleeping responses could be made. To have rendered the subjects hyperoxic during sleep would have regularized ventilation which could affect the response to increasing P_{CO_2}. Our failure to observe a further increase in the slope of the HCVR with acclimatization could have been secondary to the fact the responses on days 4 and 7 at altitude were conducted at a higher oxygen saturation than on day 1. This resulted from the higher eupnic arterial oxygen

saturation which occurred with acclimatization (Fig 2). Therefore, whether altitude acclimatization actually would have increased the slope of the response had all studies been conducted at a similar P_{O_2} remains unknown.

Our observations regarding ventilation during sleep at altitude are similar to those recently described (2). Sleep induces a decrement in ventilation at both sea level and altitude (Fig 2) and in both instances this decrement is secondary to falling tidal volume (Fig 3). This is associated with increasing P_{CO_2} and decreasing oxygen saturation. With acclimatization, increases in ventilation occur during both wakefulness and sleep which produces further hypocapnia and improved oxygenation (Fig 2). This acclimatization process seems to occur during both wakefulness and sleep as was recently described by Berssenbrugge et al (2). On the first night at altitude there appeared to be a modest increase in ventilation and steady decrement in P_{CO_2} during the sleep period (Figure 4). However, this occurred in only four of the six subjects so statistical significance was not reached. Such a trend was not observed on night 4 or 7 perhaps because the acclimatization process had slowed sufficiently at that point to be indetectable over a short period of time. These findings suggest, as shown previously (2), that wakefulness is not necessary for ventilatory acclimatization.

Of interest is the observation that ventilation during NREM and REM sleep, although slightly greater, did not increase signficantly on nights 4 and 7 compared to night 1 at altitude

(Fig 2). This occurred despite falling P_{CO_2} and increasing arterial oxygen saturation (Fig 2). This agrees with the work of Bursenbrugge et al (2) who observed no difference in ventilation during NREM and REM sleep at 21 and 83 hours after arrival at altitude. This suggests that metabolic rate may have fallen between nights 1 and 4 such that a similar level of ventilation produces greater hypocapnia. However, metabolic rate determinations during sleep were not attempted in this study.

Our findings also indicate that the majority of ventilatory acclimatization occurs as a result of increasing frequency as opposed to changes in tidal volume. As is shown in figure 3, there was a significant increase in frequency from sea level to night 1 at altitude during wakefulness and sleep, and a trend toward further increases in frequency with time at altitude. There was, however, little change in tidal volume (Fig 3). This agrees with the previous work of Burki (3) who demonstrated a steady increase in respiratory frequency with acclimatization. Other investigators have varied in their observations. Bessenbrugge et al (2) found an initial increase in tidal volume on exposure to altitude, but acclimatization occurred by increasing frequency. Gautier et al. (15) on the other hand, found an initial increase in frequency and then a steadly increase in tidal volume over 6 days. Why these studies vary so dramatically may relate to the method of determining ventilation (mouthpiece, masks, inductive plethysmography) and the timing of the study relative to arrival at altitude. However, our findings indicate that respiratory frequency is the primary mode of increasing ventilation at altitude during wakefulness and sleep.

In assessing our findings several potential weaknesses of the methods must be considered. The use of a mask to measure ventilation can produce problems (1,15) and the additional equipment in combination with this mask can be quite disruptive to sleep. This is discussed at length in the companion article (24). However, these methods were common to all studies and thus their disruptive effects would not be a likely explanation for the changes we observed at altitude. Another potential difficulty is the accurate determination of $P_{ET}CO_2$ during sleep, particularly REM sleep, when tidal volume is irratic and frequently reduced. This, however, turns out to be a minimal problem. During hypercapnic ventilatory responses, respiration is stimulated and the inspired-expired CO_2 difference is small such that accurate P_{CO_2} values can be obtained. At altitude ventilation is also stimulated such that good end-tidal CO_2 plateaus occur and reproducible results are generally observed. Our criteria for inclusion of hypercapnic venitlatory response data could also be questioned and is discussed in the companion article.

We conclude that acclimatization to high altitude has clear effects on chemical sensitivity. The hypoxic response increases over time at altitude and the hypercapnic response shifts to the left. These events, particularly the increasing hypoxic sensitivity, may be pivotal in the acclimatizatin process.

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The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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TABLE 1

The Effect of Sleep and Altitude on the Hypercapnic Ventilatory Responsiveness.

HYPERCAPNIC VENTILATORY RESPONSE

SUBJECT	AWAKE				NREM SLEEP				REM SLEEP			
	SL	1	4	7	SL	1	4	7	SL	1	4	7
1	1.18	9.05	8.71	6.97	1.02	2.37	2.87	2.49	.84	.48	1.12	1.55
2	1.86	3.51	4.10	5.75	1.26	1.98	4.02	4.50	.77	1.23	1.49	1.74
3	1.35	3.20	-	-	.51	2.13	-	-	.24	-	-	-
4	2.70	4.40	4.00	4.64	.78	1.98	1.02	1.73	.31	.72	.34	1.35
5	0.91	3.06	5.77	5.92	.96	1.29	1.33	2.90	-	.44	.58	.96
6	0.87	2.87	5.94	6.94	.84	1.50	2.10	1.35	.71	-	1.60	-
MEAN ± SEM	1.48 ± .28	4.35* ± .97	5.70* ± .85	6.04* ± .43	.90† ± .10	1.88*† ± .16	2.27*† ± .54	2.59*† ± .55	.57† ± .12	.72† ± .18	1.03† ± .25	1.40† ± .17
Mean Number of Studies per Person Completed ± SEM	2 ± -	1 ± -	1 ± -	1 ± -	3.8 ± .6	2.3 ± .3	3.2 ± .4	3.2 ± .6	2.0 ± .3	.7 ± .2	1.4 ± .2	1.6 ± .4

All values are the slope of increasing ventilation (L/min) versus increasing P_{CO_2} (mmHg).

SL, sea level.

* $P < 0.05$ different from sea level values for the same sleep stage or wakefulness.

† $P < 0.05$ different from awake values on the same study night.

TABLE 2

The Influence of Altitude Acclimatization on the Postion of the Hypercapnic Ventilatory Response During Wakefulness and Sleep

	Awake	NREM	REM
Sea Level	44.1±.4	45.5±.8	44.6±.8
1st Night Altitude	38.3±.8*	37.6±.8*	37.1±1.0*
4th Night Altitude	34.6±1.0*†	34.9±.6*†	34.0±.5*†
7th Night Altitude	33.5±.3*†	34.9±.4*†	34.2±.5*†

All values are the "ventilation stimulation point" (P_{CO_2} in mmHg) as described in the methods and Figure 1.

Means ± SEM's are given.

* $P < 0.05$ different from sea level value for the sleep stage in question.

† $P < 0.05$ different from 1st night at altitude.

TABLE 3

The Influence of Altitude Acclimatization on the Hypoxic Ventilatory Response

			Day At Altitude							
	Sea Level		1		4		7		19	
Subj	S	PCO_2	S	PCO_2	S	PCO_2	S	PCO_2	S	PCO_2
1	.41	40.8	.93	39.4	1.28	33.5	2.07	32.1	2.50	30.1
2	.88	39.5	.59	33.9	1.21	34.0	1.60	33.7	-	-
4	.29	37.6	.43	36.3	.69	31.0	.70	31.5	1.89	29.8
5	.51	40.4	.40	39.9	.62	34.4	2.23	33.4	7.17	32.9
6	.17	40.4	.27	39.1	.81	35.2	1.57	33.9	2.55	33.3
7	.31	39.5	3.17	36.5	3.05	34.5	-	-	12.74	33.2
MEAN ± SEM	.60 ± .17	39.7 ± .5	.97 ± .45	37.5 ± 1.0	1.28 ± .38	33.8 ± .6	1.63 ± .27	32.9 ± .5	5.37 ± 2.07	31.9 ± .8

S, slope of ventilation versus arterial oxygen saturation; P_{CO2}, the P_{CO_2} level at which the study was conducted.

Subject 3 was not included in data analysis as results were only available from day 1 at altitude. Subject 7 participated in only hypoxic ventilatory response testing and no other studies. The correlation between time at altitude and hypoxic response, using the Spearman Rank correlation for montonic trend (not necessarily linear) was highly significant, $P<.001$.

FIGURE LEGENDS

Figure 1 — The "ventilation stimulation point" is demonstrated. This represents the point at which ventilation is first stimulated by increasing P_{CO_2}. The point is used to describe the position of the hypercapnic ventilatory response rather than the traditional B which is a product of both the position and slope of the response.

Figure 2 — The influence of sleep and altitude acclimatization on ventilation ($\dot{V}_E$), P_{CO_2}, and arterial oxygen saturation ($Sa0_2$) are depicted. All values are means ± SEM. During sleep, ventilation fell with increasing P_{CO_2} and decreasing $Sa0_2$. With acclimatization, there was a steady increase in ventilation and $Sa0_2$ with falling P_{CO_2}.

* $P<0.05$ different from awake value.

† $P<0.05$ different from sea level value.

+ $P<0.05$ different from 1st night at altitude value.

§ $P<0.05$ different from 4th night at altitude value.

Figure 3 The influence of sleep and altitude acclimatization on ventilatory pattern (frequency and tidal volume) are depicted. All values are means ± SEM. Ventilatory acclimatization tended to occur by increasing frequency with little change in tidal volume. The fall in ventilation noted during sleep was generally a product of falling tidal volume.

* P <0.05 different from awake value.

† P <0.05 different from sea level value.

+ P <0.05 different from 1st night at altitude value.

Figure 4 The influence of acclimatization on ventilation and P_{CO_2} during sleep on the fist night at altitude is depicted.

A: The mean sleeping (NREM and REM) P_{CO_2} ±SEM value for four subjects during the 1st, 2nd, and 3rd parts of the night are shown. There is a trend toward decreasing P_{CO_2} over the course of the night.

B: The mean ventilation and P_{CO_2} values for subject 6 at various time during the first night at altitude are shown. This subject was chosen as a large quantity of data was available.

Figure 5 The influence of sleep and altitude acclimatization on the hypercapnic ventilatory response are shown. Each line represents the mean value for all subjects studied. Sleep consistently reduced the hypercapnic response with the lowest values being seen during REM sleep. Although altitude responses were greater than sea level ones, the response did not increase with time at altitude, although it did shift to the left.

Figure 6 The influence of altitude acclimatization on the hypoxic ventilatory response for each subject is shown. SL indicates sea level and the number beside each response indicates the night at altitude on which the study was conducted. $\dot{V}_E$, expired ventilation in L/min; $Sa0_2$, arterial oxygen saturation in %.

Figure 7 The influence of altitude and acclimatization on the mean hypoxic ventilatory response (±SEM) is shown. There was a steady increase in hypoxic sensitivity with time at altitude ($P<.001$ correlation between time and hypoxic response - see Data Analysis).

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